

USER'S GUIDE

Biomarkers Database

I. INTRODUCTION

As part of EPA's Biomarkers of Environmental Health and Safety Risks to Children for Use in a Longitudinal Cohort Study Task, a literature search was conducted. The references obtained from the literature search were stored electronically in a Microsoft Access97 database. Reviews of the references and abstracts were also stored in the database. In addition to a summary report on the literature search, this database (referred to as the Biomarkers Database) was delivered to EPA on June 14, 2002.

The literature search focused primarily on peer-reviewed literature, using MedLine as the main source of information. References were obtained for articles that met the search criteria summarized in Table 1 (the full search strings are listed in Appendix A).

Each reference and its abstract was reviewed and screened in terms of relevancy to EPA's goals. To pass the initial review, the title and/or abstract must have met the following criteria:

1. A review article, or a recent primary study, or a primary study on an emerging topic that is not elsewhere reviewed in the literature.
2. Contained (or at least presented an adequate impression that the full article may provide) the following data in humans, mammals, or birds (any life stage):
 - at least one biomarker of exposure, susceptibility or effect (terms defined in Appendix B); and
 - an adverse health outcome (while the focus was on cancer, respiratory health/asthma, developmental disability/autism, and unintentional injury, other health outcomes were included as well).

Note: An exposure did not have to be discussed in the title/abstract to pass the screen. All exposures were considered relevant, with the exception of medical treatments.

3. Published in the time period designated for the health outcome category, as described above. Some references outside the designated time periods were passed, e.g. to include a biomarker not previously identified.

References that did not meet these criteria were marked as Cannot Ascertain or Fail. The Cannot Ascertain result code meant that the title and/or abstract were not detailed enough to determine whether the criteria were met or not. The Fail result code meant that the abstract did not meet the criteria. For some of the references that were marked as Cannot Ascertain, a further review was conducted on the article to determine if the criteria were met and a new result code was given.

Table 1. Summary of Keyword Search Strings and Search Limitations

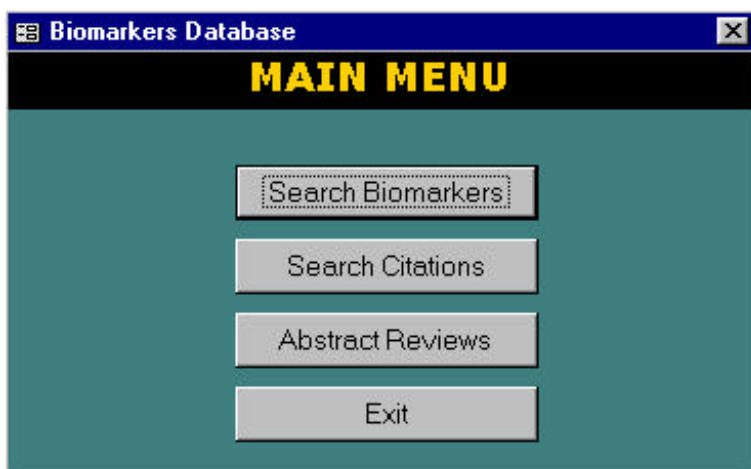
Category	Keyword Search Strings	Limitations
General	1. biomarker AND exposure AND environmental pollution. 2. molecular epidemiology 3. biomonitor AND exposure 4. genetic marker AND biomarker 5. predisposition to disease AND biomarker 6. metabolite AND exposure 7. fetus AND biomarker 8. pregnancy complication AND biomarker	1999-2001; Review “ “ ” ” ” 2000-2002 “
Exposure	9. pesticides AND biomarker 10. air pollution AND biomarker 11. effect biomarker AND exposure 12. susceptibility biomarker AND exposure	1999-2001; Review 10/01/02 to 4/10/02 All “ 1999-2001; Review “
Asthma	13. asthma AND biomarker 14. respiratory health AND biomarker 15. asthma AND biomarker AND exposure 16. respiratory tract diseases AND biomarker	1999-2001; Review 10/01/02 to 4/10/02 All 1999-2001; Review “
Cancer	17. cancer AND biomarker 18. cancer AND biomarker AND pregnancy 19. cancer AND biomarker AND pregnancy AND exposure	1999-2001; Review, Child 0-18 1999-2001; Review “
Neurodevelopmental Disorders	20. autism AND biomarker 21. neurodevelopmental disorder AND exposure 22. developmental disability AND biomarker 23. neurotoxic* AND biomarker 24. neurological development AND biomarker	1996-2001; Review 10/01/02 to 4/10/02 All “ “ 1999-2001; Review “
Injury	25. injury AND biomarker 26. injury AND exposure AND adverse effects 27. coordination AND biomarker AND exposure 28. impulsive behavior AND biomarker AND exposure	1996-2001; Review Child 0-18 “ 1999-2001; Review “
Miscellaneous		2000-2002; Review or representative reference

The Biomarkers Database contains all references obtained during the literature search, including those abstracts marked as Cannot Ascertain or Fail. It has 1874 citations with abstracts and some basic information extracted from each abstract text. The default setting for the search procedures described below is the set of 849 references that met the criteria above and passed the screen.

II. BIOMARKERS DATABASE

The Biomarkers Database was designed to serve three purposes: (1) to allow users to search the biomarker records compiled, (2) to allow users to search the citations file, and (3) to allow users to read the abstract reviews. Only references that passed the screening criteria are accessed during the default search procedure. This default can be changed on the Biomarkers Search and the Citations Search screens. The Abstract Reviews screen lists all references in the database.

Figure 1. Database Main Menu



Two versions of the Biomarkers Database were provided to EPA. One version allows the user to view the contents of the database without making any modifications or additions. The other 'editable' version allows users to modify the database's contents and to add additional references.

Both versions of the database require the user's computer to have Microsoft Access installed. Since the databases were developed in Microsoft Access 97, this is the preferred version of Access to use. However, newer versions of Access should be able to run it. If you are not using Access97, you may get a message about converting the database to the newer version of Access upon opening the database. It is recommended that you do NOT convert the database.

A. THE BIOMARKER SEARCH

Most of the biomarker information recorded in the database was obtained from abstracts. During the abstract review process, each reviewer recorded in the Biomarker Information form (see Figure 8) the name of any biomarker(s) that were discussed in the reference's abstract. In addition, if available, the biomarker type, health outcome, specimen type, and exposure were recorded.

The Biomarker Search procedure allows researchers to search the Biomarkers table in the database by defining a search term for one or more fields. In the Main Menu screen, press the

Search Biomarkers button. Figure 2 shows what the Search Biomarkers screen looks like. More specifics on the biomarker search procedure are discussed below.

Figure 2 Search Biomarkers Screen

Biomarkers [X]

SEARCH BIOMARKERS

Enter Search Term in Any or All Fields

Biomarker Name []

Health Outcome Category []

Health Outcome Description []

Biomarker Type []

Exposure []

Specimen Type []

☒ Passed Articles Only

[Search] [Clear] [Close]

Fields to Search

The user can specify search terms for any or all of the following fields: Biomarker Name, Health Outcome Category, Health Outcome Description, Biomarker Type, Exposure, or Specimen Type. Fields with a down arrow on the right have dropdown menus from which the user may select the search term. While the Biomarker Name field has a dropdown list, the user can also type in a particular text string that they are looking for in the biomarker name field (e.g., cyp).

Search Term

For fields where the user types in the search term (Biomarker Name, Health Outcome Description, and Exposure), the search term has to be either (1) one word/text string or (2) an exact phrase (e.g., genetic composition). The search engine is not designed to perform a search of multiple terms for one field (e.g., CYP-2A6 and CYP-genes).¹ When conducting searches, it is important to note that the search engine does not include automatic mapping to similar terms. For example, entry of the term "biomarker" does not automatically map to the term "biological marker. Therefore, using alternative terms or text strings may increase search yields.

¹ Users wanting to conduct complex searches are recommended to use the Microsoft query tools.

Search Strategy

The search procedure is designed to allow a search term to be entered into each field of interest. For example, a search can be done that looks for articles on the CYP-2AG biomarker where the health outcome category is Cancer.

A new search can be initiated by simply pressing the Clear button. Previous searches are not saved.

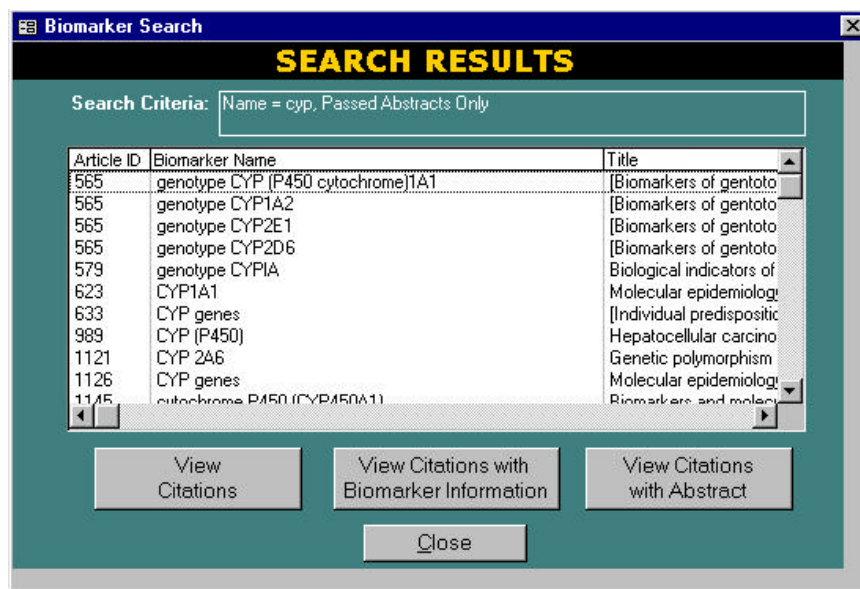
Also, the user can specify whether the search is to be conducted only on abstracts that passed the review process (which is the default) or on all abstracts in the database. To search all records, the user must uncheck the Passed Articles Only option at the bottom of the screen. However, in general, there are no biomarkers listed for the articles marked Cannot Ascertain or Fail.

Search Results and Reports

After entering the search terms, hit the Search button. A Search Results table (Figure 3) will be displayed. The search criteria will be listed in the box at the top of the screen.

The following fields appear in the Results Table: Article ID, Biomarker Name, and Article Title. The Article ID is unique to the Biomarkers Database – it has no relation to MedLine identification numbers. Also, the same article will appear on multiple rows in the Search Results table, if there are multiple biomarkers associated with the article; however, in the Reports section the citation will only appear once.

Figure 3. Biomarkers Search Result Screen



The Search Results page allows the user to generate a report for: (a) all titles in the list, (b) a highlighted title, or (c) multiple highlighted titles. The various reports include:

- A printout of citations only
- A printout of citations with biomarker information
- A printout of citations with abstract

Prior to selecting the report to view, the user must highlight the references to be included in the report. For articles with multiple biomarkers recorded, all biomarkers must be highlighted for them to appear in the report of 'Citations with biomarker information.' In addition, for articles with many biomarkers recorded, the biomarker report will only include biomarkers meeting the search criteria. To view all biomarker information recorded for a reference, the user will have to use the Citations Search procedure or go through the Abstract Review Form.

After selecting the report to view, the report will be displayed on the screen. To print the report, the user just has to go to the menu bar at the top of the window and select File, then Print. The standard Windows print menu will appear. Examples of the reports are provided in Appendix C.

B. THE CITATIONS SEARCH

All of the citation information was obtained from the abstract databases used to conduct the literature search (this most often was MedLine). No revisions or additions were made to this information.

The Search Citations procedure is conducted on the citations compiled from the literature search. The search procedure is very similar to the method described under the biomarker search. The citations search procedure will allow the researcher to search multiple fields by defining a search term for each field. Figure 4 shows what the Search Citations screen looks like. More specifics are discussed below.

Figure 4. Search Citations Screen

The screenshot shows a Windows-style window titled "Citations". Inside the window, the title "SEARCH CITATIONS" is displayed in bold yellow text on a black background. Below this, a yellow rectangular box contains the instruction "Enter Search Term in Any or All Fields". Underneath this box are five input fields arranged vertically, each with a label to its left: "Title", "Author", "Journal", "Year", and "Keyword". The "Keyword" field contains the text "cancer". Below the input fields is a checkbox labeled "Passed Abstracts Only", which is checked. At the bottom of the window are three buttons: "Search", "Clear", and "Close".

Fields to Search

The user can specify search terms for any of the following fields: Title, Author, Journal, Year of Publication, or Keyword. Fields with down arrow keys (i.e., Journal, Year) have dropdown menus from which the user must select a search term.

Search Term

For fields where the user types in the search term (Title, Author, and Keyword), the search term has to be (1) one word/string or (2) an exact phrase (e.g., genetic composition). The search engine is not designed to perform a search of multiple terms for one field (e.g., cancer AND skin).

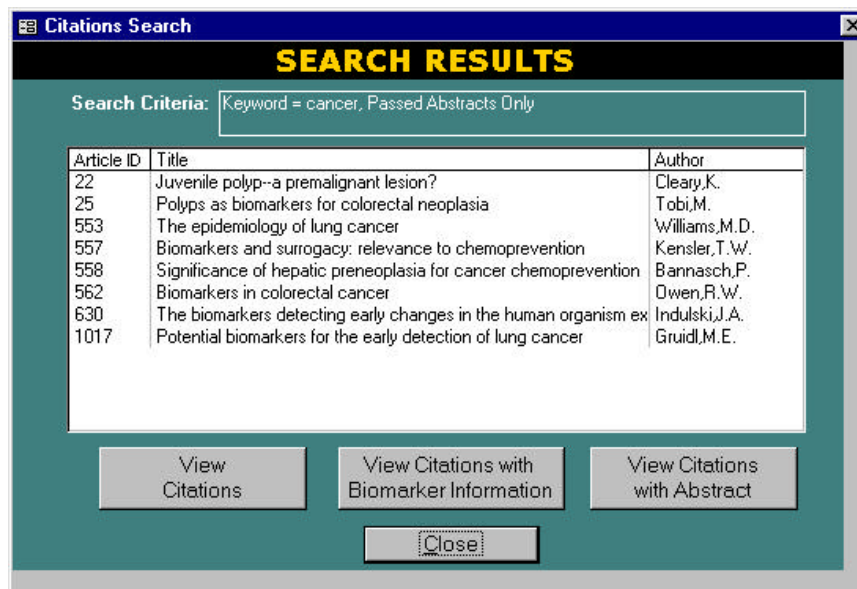
Search Strategy

The search procedure is designed to allow a search term to be entered for any or all fields. Also, the user can specify whether the search is to be conducted only on abstracts that passed the review process (which is the default) or on all abstracts in the database.

Search Results and Reports

A Search Results table (see Figure 5) will be displayed to the user. The following fields appear in the results table: Article ID, Article Title, and Author.

Figure 5. Citations Search Results



Article ID	Title	Author
22	Juvenile polyp--a premalignant lesion?	Cleary,K.
25	Polyps as biomarkers for colorectal neoplasia	Tobi,M.
553	The epidemiology of lung cancer	Williams,M.D.
557	Biomarkers and surrogacy: relevance to chemoprevention	Kensler,T.W.
558	Significance of hepatic preneoplasia for cancer chemoprevention	Bannasch,P.
562	Biomarkers in colorectal cancer	Owen,R.W.
630	The biomarkers detecting early changes in the human organism ex	Indulski,J.A.
1017	Potential biomarkers for the early detection of lung cancer	Gruidl,M.E.

The search results page allows the user to generate a report for: (a) all titles in the list, (b) a highlighted title, or (c) multiple highlighted titles. The various reports include:

- A printout of citations only
- A printout of citations with biomarker information
- A printout of citations with abstract

Prior to selecting the report to view, the user must highlight the references to be included on the report. After selecting the report to view, the report will be displayed on the screen. To print the report, the user just has to go to the menu bar at the top of the window and select File, then Print. The standard Windows print menu will appear. Examples of the reports are provided in Appendix C.

C. THE ABSTRACT REVIEW OPTION

The third main feature of the database is the ability to read (and for the editable database, to record) notes from a review of the article and/or its abstract. These review forms are similar to those used by project staff during abstract and article review.

There are three review forms:

- The Abstract Review form is used to record whether the article may be relevant to this task. Every abstract in the biomarker database will have a pass, fail, or not ascertained result code on this form.
- The Biomarker Information form is used to record any biomarkers referenced in the abstract along with its health outcomes and some other information. Note: Some biomarkers were added to this form during review of full articles.
- The Additional Information (Article Review) form was designed to record information obtained from reading the actual article. (This form was used very little during the initial review since few full articles were read. Thus there is often little to no information recorded. However, the form has been retained in the database for possible future use by EPA.)

To read the review for an abstract, the user first selects an article title of interest from a list of all citations in the database by clicking on the left mouse key.

Figure 6. Abstract List for Review

Biomarkers Abstract List

SELECT ABSTRACT FOR REVIEW

ArticleID	Result	Title	Authors
1	Pass	Potential diagnostic aids for abnormal fatty	Ward,P.E.
2	Pass	Research on screening and diagnosis in au	Bristol-Power,M.M.
3	Pass	Genetic susceptibility to neurodevelopment	Ryan,S.G.
4	Pass	Childhood risk factors for atopy and the imp	Wahn,U., von Muti
5	Pass	Immunology of respiratory syncytial virus in	Welliver,R.C.
6	Pass	Inflammatory markers in clinical practice	Wilson,N., Pederse
7	Pass	Sampling methods: urine/blood analysis	Koller,D.Y.
8	Pass	Gas analysis	de Jongste,J.C., Al
9	Pass	Biochemical measurements of bone turnover	Szule,P., Seeman

Record: 1 of 201

Open Review Form Preview Abstract Print Abstract Close

After highlighting the title, the user would click on 'Open Review Form.' The abstract review form will then be displayed (see Figure 7). The citation, abstract, and review will be displayed on the computer screen.

Figure 7. Abstract Review Form

Abstract Review

ABSTRACT SUMMARY (Click on abstract to read full summary)

Article ID: 1

Title: Potential diagnostic aids for abnormal fatty acid metabolism in a range of neurodevelopmental disorders

Author(s): Ward,P.E.

Journal: Prostaglandins Leukot.Essent.Fatty Acids Year: 2000/07//

Keywords: Apraxias, Attention Deficit Disorder with Hyperactivity, Autistic Disorder, Biological Markers, blood, Breath Tests, Child, Comorbidity, diagnosis,

Abstract: Disorders of neurodevelopment include attention deficit hyperactivity disorder, dyspraxia, dyslexia and autism. There is considerable co-

ABSTRACT REVIEW

Reviewer: Westat

Date Screened: 11/8/01 Today

Screen Result: Pass

Reason for Failure:

Publication Type: Review article, chapter - general

Biomarker Info Additional Info Save Review Close

From the Abstract Review form, the user can choose to view the biomarker information collected from the current reference (Figure 8) or go to the Additional Information form to see the article review notes, if applicable (Figure 9).

Figure 8. Biomarker Information Form

BIOMARKER INFORMATION Article ID: 1

Biomarker Name: Measures of lipid metabolism

Biomarker Type?: Effect

Exposure Indicated:

Health Outcome Category: ☐ Cancer ☐ Respiratory ☒ Neurodevelopmental ☐ Injury ☐ Other

SPECIFY Health Outcome: Autism, attention deficit hyperactivity disorder, dyspraxia, dyslexia

Intermediate/Subclinical Endpoint:

Specimen Type: Not Specified Blood Urine Saliva/ buccal cells

Display Abstract Save Record New Record Get Record Delete Record Close Form

Figure 9. Additional Information Form

ARTICLE REVIEW (Note: To expand box for writing, press Shift-F2)

Article ID: 1 **Article Screen Result:**

Reviewer: **Reason for Failure:**

Date Reviewed: Today

Study Species: Select: Human Mammal

Specimen Type: Blood Urine Saliva/ buccal ce Nasal lavage Hair Bone

Specimen Degradation:

Biomarker Measurement Technique(s):

New Measurement Method(s) Being Explored:

Invasive/ Noninvasive:

Precision/ Reliability/ Required Sample:

Specimen Sample Size:

Collection Conditions:

Comments on Future Use(s): Disorders of neurodevelopment (attention deficit hyperactivity disorder,

Display Abstract Save Close

The Biomarker Information (Figure 8) form will appear blank upon opening it. The instructions now differ between the editable and non-editable versions of the database, so each is described separately below.

Non-editable Version

In the non-editable version of the database, to view the list of biomarkers discussed in the reference, you would click on the biomarker name dropdown menu. To pull up information on a particular biomarker, just click on its name. The information available for that biomarker will appear in the other fields. Note: The Save Record, New Record, and Get Record buttons are turned off in the non-editable version.

Editable Version

In the editable version of the database, to see what biomarker information is available in the reference, click on the 'Get Record' button. This will display a form with a list of the biomarkers discussed in the reference. Highlighting the biomarker of interest will bring up its information in the Biomarker Information form. To add a new biomarker to the reference (e.g., after reading the full article), the user would fill in the blank form with all available information.

In the editable version, the user may also add additional information to the Additional Information form. Simply close the Biomarker Information form and open the Additional Information form.

Only the editable version of the database will allow the user to add a new reference to the database. The main menu of the editable database has an option to add a citation. This option will bring up a screen for the user to type in the new citation and all of its accompanying information. Once the reference is added to the database, it cannot be edited nor deleted.

Appendix A

Pub Med Search String Details and Limitations

Category	Search Terms and Pub Med Search Details	Limitations
General	biomarker* or biological Markers [MESH] AND exposure AND environmental pollution ("biological markers" [MESH Terms] OR biomarker [TEXT Word]) AND exposure[All Fields])	1999-2001; Review
	molecular epidemiology ("epidemiology, molecular"[MeSH Terms] OR molecular epidemiology[Text Word])	1999-2001; Review
	biomonitor* AND expos* (biomonitor[All Fields] OR biomonitored[All Fields]) OR biomonitoring[All Fields] OR biomonitor[All Fields] OR biomonitor[All Fields] AND (expos[All Fields])	1999-2001; Review
	genetic marker* AND biomarker* OR "biological markers"[MAJR] (genetic marker[All Fields] OR genetic markers[All Fields]) OR genetic markers/analysis[All Fields]) OR genetic markers/blood[All Fields]) OR genetic markers/genetics[All Fields]) OR genetic markers/immunology[All Fields]) OR genetic markers/physiology[All Fields]) OR genetic markers/urine[All Fields]) AND ((biomarker[All Fields] OR biomarker/polymerase[All Fields]) OR biomarkers[All Fields])) OR "biological markers"[MeSH Major Topic])	1999-2001; Review (biological markers term limited to major point of article)
	predisposition to disease AND biomarker* OR "biological markers"[MAJR] ("disease susceptibility"[MeSH Terms] OR predisposition[Text Word]) AND ("disease"[MeSH Terms] OR disease[Text Word])) AND ((biomarker[All Fields] OR biomarker/polymerase[All Fields]) OR biomarkers[All Fields])) OR "biological markers"[MAJR])	1999-2001; Review (biological markers term limited to major point of article)
	metabolit* AND expos* (metabolit* [ALL Fields of ALL words containing metabolit]) AND (expos*[ALL fields of ALL words containing expos])	1999-2001; Review
	fetus AND biomarker ("fetus"[MeSH Terms] OR fetus[Text Word]) AND ("biological markers"[MeSH Terms] OR biological marker[Text Word])	2000-2002

Category	Search Terms and Pub Med Search Details	Limitations
General, cont.	pregnancy complications AND biomarker ("pregnancy complications"[MeSH Terms] OR pregnancy complications[Text Word]) AND ("biological markers"[MeSH Terms] OR biomarker[Text Word])	2000-2002
	pregnancy outcome AND biomarker ("pregnancy outcome"[MeSH Terms] OR pregnancy outcomes[Text Word]) AND ("biological markers"[MeSH Terms] OR biomarker[Text Word])	2000-2002
Exposure	pesticides[MESH] OR pesticide* AND "biological Markers"[MESH] OR biomarker* ("pesticides"[MeSH Terms] OR (pesticide[All Fields] OR pesticide/animal[All Fields]) OR pesticide/herbicide[All Fields]) OR pesticide/m2[All Fields]) OR pesticide/solvent[All Fields]) OR pesticideformulating[All Fields]) OR pesticides[All Fields]) OR pesticides/analysis[All Fields]) OR pesticides/blood[All Fields]) OR pesticides/chemistry[All Fields]) OR pesticides/classification[All Fields]) OR pesticides/commodities[All Fields]) OR pesticides/economics[All Fields]) OR pesticides/fertilisers[All Fields]) OR pesticides/fertilizer[All Fields]) OR pesticides/history[All Fields]) OR pesticides/immunology[All Fields]) OR pesticides/metabolism[All Fields]) OR pesticides/metabolites[All Fields]) OR pesticides/pharmacokinetics[All Fields]) OR pesticides/pharmacology[All Fields]) OR pesticides/poisoning[All Fields]) OR pesticides/standards[All Fields]) OR pesticides/toxicity[All Fields]) OR pesticides/urine[All Fields]) OR pesticides/weedicides[All Fields])) AND "biological Markers"[MESH]) OR (biomarker[All Fields] OR biomarker/polymerase[All Fields]) OR biomarkers[All Fields])*	1999-2001; Review 10/01/01 to 4/10/02 All Pubs
	effect biomarker AND exposure (effect[All Fields] AND ("biological markers" [MESH Terms] OR biomarker[Text Word]) AND exposure[All Fields])	1999-2001; Review
	susceptibility biomarker AND exposure ("disease susceptibility"[MESH Terms] OR Susceptibility[Text Word]) AND ("biological markers"[MESH Terms] OR biomarker [Text Word]) AND exposure[All Fields])	1999-2001; Review

Category	Search Terms and Pub Med Search Details	Limitations
Exposure, cont.	"air pollution"[MESH] OR "air pollutants" [MESH] OR air pollut* AND "biological markers" [MESH] Or biomarkers* ("air pollution"[MESH] OR "air pollutants"[MESH]) OR (air pollutant[All Fields] OR air pollutants[All Fields]) OR air pollutants/analysis[All Fields]) OR air pollutants/blood[All Fields]) OR air pollutants/chemistry[All Fields]) OR air pollutants/classification[All Fields]) OR air pollutants/economics[All Fields]) OR air pollutants/history[All Fields]) OR air pollutants/immunology[All Fields]) OR air pollutants/metabolism[All Fields]) OR air pollutants/pharmacokinetics[All Fields]) OR air pollutants/pharmacology[All Fields]) OR air pollutants/poisoning[All Fields]) OR air pollutants/standards[All Fields]) OR air pollutants/toxicity[All Fields]) OR air pollutants/urine[All Fields]) OR air polluted[All Fields]) OR air polluting[All Fields]) OR air pollution[All Fields]) AND "biological markers"[All Fields])	1999-2001; Review 10/01/01 to 4/10/02 All Pubs
Asthma	asthma AND biomarker ("asthma"[MESH Terms] OR asthma[Text Word]) AND ("biological markers"[MESH Terms] OR biomarker[Text Word])	1999-2001; Review 01/01/02 to 4/10/02 All Pubs
	respiratory health AND biomarker (respiratory[All Fields] AND ("health"[MESH Terms] OR health[Text Word]) AND ("biological markers"[MESH Terms] OR biomarker [Text Word])	1999-2001; Review 10/01/02 to 4/10/02 All Pub
	asthma AND biomarker AND exposure asthma AND exposure[All Fields] AND biomarker* OR biological Markers [MESH]	1999-2001; Review
	"respiratory tract diseases" [MAJR] OR asthma AND "biological Markers" [MESH] OR biomarker* ("respiratory tract diseases"[MAJR] OR ("asthma"[MeSH Terms] OR asthma[Text Word])) AND "biological Markers"[MESH]) OR ((biomarker[All Fields] OR biomarker/polymerase[All Fields]) OR biomarkers[All Fields])	1999-2001; Review

Category	Search Terms and Pub Med Search Details	Limitations
Cancer	cancer AND biomarker ("neoplasms"[MESH Terms] OR cancer [Text Word]) AND ("biological markers"[MESH Terms] OR biomarker[Text Word])	1999-2001; Review, Child 0-18
	cancer AND biomarker AND pregnancy ("neoplasms"[MESH Terms] OR cancer [Text Word]) AND ("biological markers"[MESH Terms] OR biomarker[Text Word])	1999-2001; Review
	cancer AND biomarker AND pregnancy AND exposure (biomarker* OR biological markers) AND (cancer OR neoplasms) AND pregnancy	1999-2001; Review
Neurodevelopmental Disorders	autism AND biomarker ("autistic disorder"[MESH Terms] OR autism[Text Word]) AND ("biological markers"[MESH Terms] OR biomarker[Text Word])	1996-2002; Review 10/01/01 to 4/10/02 All Pubs
	neurodevelopmental disorders AND exposure (neuro[All Fields] AND ("developmental disabilities"[MESH Terms] OR developmental disorders[Text Word]) AND exposure[All Fields])	1996-2002; Review 10/01/01 to 4/10/02 All Pubs
	developmental disability AND biomarker ("developmental disabilities"[MESH Terms] OR Developmental disabilities[Text Word]) AND ("biological markers"[MESH Terms] OR biomarker[Text Word])	1996-2002; Review 10/01/01 to 4/10/02 All Pubs
	neurotoxicity OR neurotoxicology AND biomarker ("neurotoxicity syndromes"[MeSH Terms] OR neurotoxicity[Text Word]) OR neurotoxicology[All Fields]) AND ("biological markers"[MeSH Terms] OR biomarker[Text Word])	1999-2001; Review
	neurological development AND biomarker (neurological[All Fields] AND ("growth and development"[MeSH Subheading] OR "human development"[MeSH Terms] OR development[Text Word])) AND ("biological markers"[MeSH Terms] OR biomarker[Text Word])	1999-2001; Review
Category	Search Terms and Pub Med Search Details	Limitations

Injury	injury and biomarker ("wounds and injuries"[MESH Terms] OR injury [TEXT Word]) AND ("biological markers"[MESH Terms] OR biomarker [Text Word])	1996-2001; Review, Child 0-18
	injur* AND exposure AND adverse effects (Wounds and Injuries [MESH] OR injur*[ALL words containing injur]) AND exposure[All Fields]) AND ("adverse effects"[MeSH Subheading] OR adverse effects[Text Word])	1996-2001; Review, Child 0-18
	biological marker [MESH] coordination AND exposure ("biological markers"[MeSH Terms] AND ("organization and administration"[MeSH Terms] OR coordination[Text Word])) AND exposure[All Fields])	1999-2001; Review
	biological marker [MESH] or biomarker* AND impulsive behavior ("biological markers"[MeSH Terms] OR ((biomarker[All Fields] OR biomarker/polymerase[All Fields]) OR biomarkers[All Fields])) AND ("impulsive behavior"[MeSH Terms] OR impulsive behavior[Text Word])	1999-2001; Review
Miscellaneous	HOXA gene GABA Ubiquitin VIP Purkinje cells meconium saliva	2000-2002, Review or representative reference

APPENDIX B

BIOMARKER DEFINITIONS

Biomarker. A biomarker is defined as a cellular, biochemical, or molecular (or tissue) alteration that is measurable in biological media, such as human tissues, cells, or fluids; or the product of an interaction between a xenobiotic agent and some target molecule. Biomarkers include specific genes, pre-cancerous lesions or polyps, and diagnostic markers.

Biomarkers do not include markers of prognosis only, medical or clinical test results (such as from sepsis workups, bone mineral density, EEGs, or x-ray analysis), behavioral/cognitive functioning test results, or growth or other physical measurements or observations (such as birthweight, length, head circumference, or fingerprint ridge count).

Biomarkers of Exposure. Biomarkers of exposure include concentrations of the exogenous parent chemical, its metabolites, or reaction products in body fluids or tissues, e.g. blood lead, etc. *Bioindicators* reflect only the presence or absence of a substance. *Biomonitoring* provides for regular surveillance and quantification of the amount of substance present.

Biomarkers of Effect. Biomarkers of effect are measures of disease progression (e.g., biomarkers of early loss of pregnancy, benzo-pyrene-DNA adducts, antigen production, tumor secretions, gene suppression, etc.). Biomarkers measured in tumor tissue were not included, as the disease is diagnosed prior to the biomeasure, and the biomarker is used to determine prognosis rather than effect.

Biomarkers of Susceptibility. Biomarkers of susceptibility include the detection of a particular genotype or polymorphism (such as genetic markers of cancer susceptibility), or may be a precursor disease, such as precancerous colonic polyps. They may indicate the presence of or potential for subclinical disease or may indicate a potential protection against negative health effects of the exposure.

APPENDIX C

DATABASE REPORTS

The search procedures can generate three types of reports to display the search results: (a) a report with citations only, (b) a report with citations and biomarker information, (c) a report with citations and abstracts.

The first report lists only the basic citation information for the search results. See the following illustration:

Figure C-1

Biomarker Citations				
Article ID	565			Language English
Author	Pavanello, S., Clonfero, E.			
Title	[Biomarkers of genotoxic risk and metabolic polymorphism]			
Journal	Med. Lav.			
Year	2000	Volume 91	Page	431 - 469
Article ID	579			Language English
Author	Pavanello, S., Clonfero, E.			
Title	Biological indicators of genotoxic risk and metabolic polymorphisms			
Journal	Mutat. Res.			
Year	2000	Volume 463	Page	285 - 308
Article ID	623			Language English
Author	Sram, R.J., Binkova, B.			
Title	Molecular epidemiology studies on occupational and environmental exposure to mutagens and carcinogens, 1997-1999			
Journal	Environ. Health Perspect.			
Year	2000	Volume 108 Suppl 1	Page	57 - 70
Article ID	633			Language English
Author	Butkiewicz, D., Chorazy, M.			
Title	[Individual predisposition to lung neoplasm--the role of genes involved in metabolism of carcinogens]			
Journal	Postepy Hig. Med. Dosw.			
Year	1999	Volume 53	Page	655 - 673

The second report lists the basic citation information along with biomarker information recorded on this article. For the Citation Search, the report will include ALL biomarkers identified in the abstract. For the biomarker search, the report will only include the biomarkers that met the search criteria (e.g., those biomarkers whose biomarker name contains the term 'CYP' in it). See the following illustration:

Figure C-2

Biomarker Citations with Biomarker Information

Article ID:	565	Language: English
Author:	Pavanello, S., Clonfero, E.	
Title:	[Biomarkers of genotoxic risk and metabolic polymorphism]	
Journal:	Med. Lav.	
Year:	2000	Volume 91 Pages 431 - 469

Biomarker Name: genotype CYP (P450 cytochrome)1A1

Type: Susceptibility

Exposure: not specified

Health Outcome Category: ☐ Cancer ☐ Respiratory ☐ Neurological ☐ Injury ☒ Other

Health Outcome Description: not specified

Specimen Type: Not Specified

Biomarker Name: genotype CYP1A2

Type: Susceptibility

Exposure: not specified

Health Outcome Category: ☐ Cancer ☐ Respiratory ☐ Neurological ☐ Injury ☒ Other

Health Outcome Description: not specified

Specimen Type: Not Specified

The last report lists the basic citation information along with the abstract for the article. See the following illustration:

Figure C-3

Biomarker Citations with Abstract

Article ID:	623	Language: English
Primary Author:	Sram, R.J., Binkova, B.	
Title:	Molecular epidemiology studies on occupational and environmental exposure to mutagens and carcinogens, 1997-1999	
Journal:	Environ. Health Perspect.	
Year:	2000	Volume 108 Suppl 1 Pages 57 - 70

Abstract

Molecular epidemiology is a new and evolving area of research, combining laboratory measurement of internal dose, biologically effective dose, biologic effects, and influence of individual susceptibility with epidemiologic methodologies. Biomarkers evaluated were selected according to basic scheme: biomarkers of exposure--metabolites in urine, DNA adducts, protein adducts, and Comet assay parameters; biomarkers of effect--chromosomal aberrations, sister chromatid exchanges, micronuclei, mutations in the hypoxanthine-guanine phosphoribosyltransferase gene, and the activation of oncogenes coding for p53 or p21 proteins as measured on protein levels; biomarkers of susceptibility--genetic polymorphisms of genes CYP1A1, GSTM1, GSTT1, NAT2. DNA adducts measured by 32P-postlabeling are the biomarker of choice for the evaluation of exposure to polycyclic aromatic hydrocarbons. Protein adducts are useful as a biomarker for exposure to tobacco smoke (4-aminobiphenyl) or to smaller molecules such as acrylonitrile or 1,3-butadiene. Of the biomarkers of effect, the most common are cytogenetic end points. Epidemiologic studies support the use of chromosomal breakage as a relevant biomarker of cancer risk. The use of the Comet assay and methods analyzing oxidative DNA damage needs reliable validation for human biomonitoring. Until now there have not been sufficient data to interpret the relationship between genotypes, biomarkers of exposure, and biomarkers of effect for assessing the risk of human exposure to mutagens and carcinogens.

Keywords

analysis, Animal, Carcinogens, Comet Assay, Dna, DNA Adducts, DNA Damage, Environmental Exposure, Epidemiologic Studies, epidemiology, Epidemiology/Molecular, Genotype, Human, Hydrocarbons, Laboratories, methods, Mutagens, Mutation, Occupational Exposure, Oncogenes, Proteins, Research, Risk, Sister Chromatid Exchange, Smoke, statistics & numerical data, Support, Non-U.S. Gov't, Tobacco, toxicity, urine